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10/525,000	02/17/2005	Roland Suck	MERCK-2975	2809

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,000	SUCK ET AL.	
	Examiner	Art Unit	
	Nora M. Rooney	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *7-11,16 and 18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,12-15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/17/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-21 are pending.

2. Applicant's election with traverse of Group I, claims 1-6, 12-15 and 17 and the species of SEQ ID NO:2 in the reply filed on 07/17/2007 is acknowledged. The traversal is on the ground(s) that Cosgrove is not drawn to the instantly claimed Phi p 1 variant because SEQ ID NO: 20 of Cosgrove exhibits "40.7 % sequence identity over amino acids 14-239 of SEQ ID NO: 2" and further contains "61 mismatches and 21 inserted amino acids" further corroborates this distinction. Further, Applicants argue that the entirety of the present claims possess unity of invention under 37 C.F.R. §1.499 because the claims in the instant application involve related subject matter, for example, a grass pollen allergen, as recited in Applicants' elected Group I. All the claims would comprise overlapping subject matter Applicant argues, so it would not be an undue burden on the Examiner to carry out a search.

This is not found persuasive because Cosgrove et al. teaches a Phl p 1 variant as encompassed by the language of the claim recitations of Group I. Phl p 1 variants may have additions, subtractions and substitutions and still be variants. Therefore, the claims do not contribute a special technical feature over the prior art and lack unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 7-11, 16 and 18-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07/17/2007.

4. Claims 1-6, 12-15 and 17 are currently under examination as they read on a Phl p 1 variant characterizes in that it has an additional cysteine residue as compared with the wild type.

5. Applicant's IDS document filed on 02/17/2005 is acknowledged.

Claim Objections

6. Claims 1-6, 12-15 and 17 are objected to because of the following informalities:

A. Claims 1-6, 12-15 and 17 should recite 'A variant' or 'An allergen variant' instead of 'variant' or 'allergen variant.'

B. Claims 13-14 lack correct punctuation. The recited steps require commas and an 'and' or an 'or' before the last recited steps. As written, the claims are not sentences.

C. The term 'medicament' in Claim 15 lacks antecedent basis and should be 'a medicament.'

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 3-4 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-4 recite specific allergen variants by amino acids residues making the claims indefinite. An inserted reference sequence identification number to show exactly where the mutants are different from the reference sequence would make the claims definite. The claims lack the requisite structural features for the composition.

Claims 6 is indefinite because the phrase 'according to SEQ ID NO:2' is unclear. Does the sequence have to be in agreement with SEQ ID NO:2 or does the sequence have to be SEQ ID NO:2.

The term "higher" in claim 3 is a relative term which renders the claim indefinite. The term "higher" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-6, 12-15 and 17 *are* rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: the polypeptide of SEQ ID NO:2, does not provide reasonable enablement for: a **variant of the major allergen Phl p 1** from timothy grass, characterised in that it has **an additional Cys residue compared with the wild type** of claim 1; **Allergen variant** according to Claim 1, characterised in that the **additional Cys residue** is located in the **carboxyl-terminated region** of claim 2; **Allergen variant** according to Claim 1, characterised in that the **additional Cys residue** is located in a higher position than amino acid position 140 of claim 3; **Allergen variant** according to Claim 1, characterised in that the **additional Cys residue** is located between amino acid positions 230 and 240 of claim 4; **Allergen variant** according to Claim 1, characterised in that the **additional Cys residue** originates from **an amino acid exchange** of claim 5; **Allergen variant rPhl p 1-A236C** according to SEQ ID NO 2 according to claim 1, characterised in that the additional Cys residue has been introduced by exchange of Ala 236 of claim 6; **Allergen variant** according to claim l characterised in that it exists in various fold forms of claim 12; Fold form rPhl p 1-LM of the **allergen variant** according to claim 1 obtainable by carrying out the following process steps: - overexpression of **the rPhl p 1 allergen variant** provided with an His tag in a host organism, - denaturing of the inclusion bodies isolated from the host organism using

guanidinium chloride, - renaturing of the dissolved protein on a chelate affinity chromatography column, - removal of the His tag, - gel filtration, - further chelate affinity chromatography, - isolation of the target protein from the flow-through , - gel filtration of claim 13; Fold form rPhl p 1-HM of **the allergen variant according** to claim 1 obtainable by carrying out the following process steps: - overexpression of the rPhl p 1 allergen variant provided with an His tag in a host organism, - denaturing of the inclusion bodies isolated from the host organism using guanidinium chloride, - renaturing of the dissolved protein on a chelate affinity chromatography column, - removal of the His tag, - gel filtration, -further chelate affinity chromatography, - elution of the target protein with an imidazole gradient - gel filtration of claim 14; **Allergen variant** according to claim 1 **as medicament**; and **Pharmaceutical composition** comprising **an allergen variant** according to Claim 15 and/or pharmaceutically usable derivatives thereof, including mixtures thereof in all ratios, and, if desired, excipients and/or adjuvants of claim 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection

are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification has only disclosed the Phl p 1 allergen mutant consisting of SEQ ID NO:2.

The specification has not adequately disclosed any variant of the Phl p 1 molecule having any number of additions, deletions and substitutions as encompassed by the present claim recitations. The specification has provided no guidance or examples as to which allergen variants with an additional cysteine would work in the claimed invention other than the Phl p 1 allergen variant of SEQ ID NO:2. The term "variant" of a 240 amino acid protein with substitutions to any amino acid with any of the 20 naturally occurring amino acids, additions of any number of undisclosed amino acids in any position, deletion of any number of amino acids, or combinations thereof, literally results in billions of compounds. One of ordinary skill in the art would be required to perform undue experimentation to determine which allergen variants other than the allergen variant of SEQ ID NO:2 would work in the claimed invention.

The specification has also adequately disclosed any Phl p 1 allergen mutant having an additional cysteine residue as a result of an amino acid exchange of any amino acid. Further, the specification does not adequately disclose any Phl p 1 allergen mutant

having an additional cysteine residue as a result of the addition of a cysteine residue anywhere within the Phl p 1 molecule. The specification describes that the claimed allergen mutant may be used in a pharmaceutical composition for the treatment of allergies. However, the art shows that the addition of a cysteine molecule within an allergen does not always decrease IgE binding. In particular, see Schramm et al. (PTO-892, Reference V) teaches that surprisingly an allergen mutant of Phl p 5b with an additional cysteine residue does not decrease IgE binding even though the additional cysteine changes the conformation of the Phl p 5 molecule by the formation of a disulfide bond with another already present cysteine (In particular, page 2409, paragraph spanning left and right columns; page 2413, first paragraph, whole document). Therefore, because of this unpredictability, one of ordinary skill in the art would be required to perform undue experimentation to practice the claimed invention commensurate in scope with the claims.

Further, without reference to a specific sequence for the wild type, it is unclear which amino acid positions within the wild type are not currently cysteines. The wild type any naturally occurring variant of Phl p 1, including as yet unknown variants.

Also at issue is whether or not the claimed composition comprising an allergen variant would function as pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical compositions are effective for in vivo use, and the lack of predictability in the art at the time the

invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. Claims 1-6, 12-15 and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : a Phl p 1 allergen mutant consisting of SEQ ID NO:2.

Applicant is not in possession of: a **variant of the major allergen Phl p 1** from timothy grass, characterised in that it has **an additional Cys residue compared with the wild type** of claim 1; **Allergen variant** according to Claim 1, characterised in that the **additional Cys residue** is located in the **carboxyl-terminated region** of claim 2; **Allergen variant** according to Claim 1, characterised in that the **additional Cys residue** is located in a **higher position** than amino acid position 140 of claim 3; **Allergen variant** according to Claim 1, characterised in that the **additional Cys residue** is located

between amino acid positions 230 and 240 of claim 4; **Allergen variant** according to Claim 1, characterised in that the **additional Cys residue** originates from **an amino acid exchange** of claim 5; **Allergen variant rPhl p 1-A236C according to SEQ ID NO 2** according to claim 1, characterised in that the additional Cys residue has been introduced by exchange of Ala 236 of claim 6; **Allergen variant** according to claim 1 characterised in that it exists in various fold forms of claim 12; Fold form rPhl p 1-LM of the **allergen variant** according to claim 1 obtainable by carrying out the following process steps: - overexpression of **the rPhl p 1 allergen variant** provided with an His tag in a host organism, - denaturing of the inclusion bodies isolated from the host organism using guanidinium chloride, - renaturing of the dissolved protein on a chelate affinity chromatography column, - removal of the His tag, - gel filtration, - further chelate affinity chromatography, - isolation of the target protein from the flow-through , - gel filtration of claim 13; Fold form rPhl p 1-HM of **the allergen variant according** to claim 1 obtainable by carrying out the following process steps: - overexpression of the rPhl p 1 allergen variant provided with an His tag in a host organism, - denaturing of the inclusion bodies isolated from the host organism using guanidinium chloride, - renaturing of the dissolved protein on a chelate affinity chromatography column, - removal of the His tag, - gel filtration, -further chelate affinity chromatography, - elution of the target protein with an imidazole gradient - gel filtration of claim 14; **Allergen variant** according to claim 1 **as medicament**; and **Pharmaceutical composition** comprising **an allergen variant** according to Claim 15 and/or pharmaceutically usable derivatives thereof, including mixtures thereof in all ratios, and, if desired, excipients and/or adjuvants of claim 17.

The specification has only disclosed the Phl p 1 allergen mutant consisting of SEQ ID NO:2; therefore, the skilled artisan cannot envision all the contemplated nucleic acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was

not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-3, 5, 12-15 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Focke et al. (PTO-892, Reference U).

Focke et al. teaches a variant of Phl p 1 (Phl p 1 peptide) with an additional cysteine residue compared with the wild type; wherein the additional cysteine is located at the carboxyl-terminated region; wherein the additional Cys residue is located in a higher position than amino acid position 140; and wherein the additional Cys residue originates from an amino acid exchange (In particular, page 3, 'Synthesis, purification

and characterization of peptides' section, Figure 1, whole document). Focke et al. also teaches a pharmaceutical composition comprising the Phl p 1 allergen variant with CFA as an adjuvant for use as a medicament (In particular, page 4, 'Immunization of mice and rabbits' section, whole document).

Claim 12 is included in this rejection because the recitation of "characterised in that it exists in various fold forms" is an inherent property of the Phl p 1 allergen variant molecule.

Claims 13-14 are included in this rejection because the recitations of "obtainable by carrying out the following process steps: - overexpression of the rPhl p 1 allergen variant provided with an His tag in a host organism, - denaturing of the inclusion bodies isolated from the host organism using guanidinium chloride, - renaturing of the dissolved protein on a chelate affinity chromatography column, - removal of the His tag, - gel filtration, - further chelate affinity chromatography, - isolation of the target protein from the flow-through , - gel filtration" of claim 13 and "obtainable by carrying out the following process steps: - overexpression of the rPhl p 1 allergen variant provided with an His tag in a host organism, - denaturing of the inclusion bodies isolated from the host organism using guanidinium chloride, - renaturing of the dissolved protein on a chelate affinity chromatography column, - removal of the His tag, - gel filtration, -further chelate affinity chromatography, - elution of the target protein with an imidazole gradient - gel filtration" of claim 14 lend no patentable weight per se. It is noted that the present claims are directed to a product, not to a method. The patentability of a product does not

depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) See MPEP 2113. Further, once a product is fully disclosed in the art, future claims to that same product are precluded, even if that product is claimed as made by a new process.

The reference teachings anticipate the claimed invention.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 27, 2007
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